MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: Review of a report from Novartis on the usefulness of the Clozaril National Patient Registry to model the risk of agranulocytosis and severe leukopenia under different monitoring frequencies
Drug: clozapine (PID #D020525)

EXECUTIVE SUMMARY

Due to limitations of data obtained from the Clozaril National Registry (CNR), it is difficult to project the incidence rates of agranulocytosis after switching from biweekly monitoring to less frequent monitoring. CNR data on patients for whom the biweekly monitoring was implemented (patients with persistence on drug of greater than 6 months and within the most recent use cohort [cohort 3]) has captured few safety events. Because the CNR does not maintain records of patients treated with generic form of clozapine and there is a substantial loss to follow-up, the estimates from cohort 3 patients may not be applicable to all patients who are currently treated with clozapine. Moreover, using estimates from previous cohorts is also questionable because many factors have changed since initial marketing which could alter the risk for agranulocytosis in clozapine users.

Given these limitations, incidence rates of clozapine-associated agranulocytosis for a worst case and a best case scenario have been included.

BACKGROUND

Ten to thirty percent of patients with schizophrenia are not responsive to standard treatment. Clozapine was introduced to the U.S. market in 1990 for treatment of resistant patient populations with a national patient registry system (Clozaril National Registry [CNR]) requirement for the risk of agranulocytosis. A health care provider can only prescribe clozapine to patients who are enrolled in the registry. Patients can only obtain clozapine if their WBC blood count is above 3000 mm^3. Prior to October 1998, weekly monitoring of WBC blood counts was performed regardless of length of treatment with clozapine. However, after 1998, weekly monitoring was required only during the first six months of treatment (when the risk is highest), after which biweekly monitoring could be performed.

In September 2002, Novartis provided a report analyzing patients enrolled in the CNR that addressed two issues: (1) an analysis of the effect of biweekly monitoring of WBC after six months of treatment on the incidence rate of agranulocytosis and severe leukopenia and (2) an assessment whether the current biweekly blood monitoring system after six months can be changed to a less frequent monitoring regimen.

In a consult request dated 11/26/2003, ODS was asked to review the Novartis report to assess the usefulness of the CNR database for modeling the risk of agranulocytosis and severe leukopenia under different monitoring frequencies. [Note that enrolled patients are limited to patients on therapy with Clozaril brand of clozapine.]

SUMMARY OF THE NOVARTIS REPORT

The company presented the following analyses:

(1) Risk assessment of agranulocytosis among the study population;
(2) An incidence rate of agranulocytosis, severe leukopenia, and moderate leukopenia among patients treated with Clozaril for more than six months;

(3) The incidence rates of agranulocytosis, severe leukopenia and moderate leukopenia among patients treated less than 6 months;
(4) A risk assessment of agranulocytosis in the CNR cohort 3 (defined below);
(5) Projections of changes in the incidence of agranulocytosis after switching the frequency of monitoring from biweekly to either monthly or to 'no monitoring' after 6 months (Novartis submission dated February 12, 2003);
(6) A supplementary analysis (Novartis submission dated February 12, 2003) conducted to assess whether rates associated with CNR cohort 3 are representative for all clozapine users and whether observed rates are comparable with rates from previous CNR cohorts 1 and 2 (defined below).

1. Overview of risk in the study population.

As of September 1, 2002, the CNR database contained a total of 203,818 Clozaril- treated patients. The sponsor defined agranulocytosis as an absolute neutrophil count (ANC) of $\leq 500/mm^3$ or WBC $\leq 1000/mm^3$. For the purpose of estimating the incidence of severe leukopenia (WBC $< 2000/mm^3$), the number of clozapine treated patients is limited to a subset of 178,104, grouped into 3 cohorts:

● cohort 1-patients enrolled prior to April 30, 1995 (N=97,485);

● cohort 2-patients enrolled after April 30, 1995 but before October 1, 1997 (N=41,359) and six months before the introduction of biweekly monitoring,

● cohort 3-patients enrolled after October 1, 1997 (N=39,260) and subject to biweekly monitoring after 6 months of therapy.

From the subset of 178,104 cohort patients, 593 and 658 patients developed agranulocytosis and severe leukopenia, respectively. There were 22 deaths due to agranulocytosis. 69% of all severe leukopenia cases (n=451), 74% of all agranulocytosis cases (n=439), and 91% of deaths (n=20) occurred within less than six months of initiation of clozapine therapy. Thus, most cases of severe injury occurred within the first six months of beginning therapy.

Therefore, the overall incidence rates of agranulocytosis were 1.053, 0.975 and 1.36 per 1,000 patient-years for cohorts 1, 2, and 3, respectively. The overall incidence rates for severe leukopenia were 1.167, 1.150, and 1.385 per 1,000 patient-years for cohorts 1, 2, and 3, respectively. Since these cohorts are associated with different durations of treatment, the standardized incidence rates have been calculated separately. The standardized incidence rates of agranulocytosis were 1.28, 0.74 and 0.74 for cohorts 1, 2, and 3, respectively. The standardized incidence rates for severe leukopenia were 1.390, 0.912 and 0.730 per 1,000 patient-years, respectively. [The corresponding values for moderate leukopenia are not available.]

2. Incidence rates of agranulocytosis, severe leukopenia, and moderate leukopenia following 6 months of treatment.

It is postulated that less frequent monitoring may result in an increased rate of agranulocytosis. If this assumption is true, the rate of agranulocytosis whould be higher in cohort 3 than in cohorts 1 and 2. Among patients treated with clozapine for less than six months, the incidence rates for agranulocytosis were 0.347, 0.147 and 0.370 per 1,000 patient-years in cohorts 1, 2 and 3, respectively; the incidence rates for severe leukopenia were 0.456, 0.308 and 0.333 per 1,000 patient-years; and the incidence rates of moderate leukopenia were 8.760, 10.311, and 7.996 per 1,000 patient-years. These data do not support a prediction of higher rates of agranulocytosis and moderate leukopenia with a reduction in the stringency of WBC monitoring. [See Discussion]

3. Incidence rates of agranulocytosis, severe leukopenia, and moderate leukopenia at ≤ 6 months of treatment.

Given that there was no change of frequency of monitoring of patients treated with clozapine for less than 6 months, it is expected that the incidence rate of agranulocytosis whould not be different between cohorts. Nonetheless, a downward trend in successive cohorts was observed in the incidence of agranulocytosis, severe leukopenia, and moderate leukopenia across all 3 cohorts (Table 1).

Table 1. Incidence rates (per 1,000 patient-years) of agranulocytosis, severe and moderate leukopenia within six months of treatment initiation (by cohort).

	cohort 1	cohort 2	cohort 3
Agranulocytosis	7.563	4.724	3.250
Severe leukopenia	7.708	4.966	3.392
Moderate leukopenia	31.008	29.921	27.958

4. Experience of agranulocytosis risk among cohort 3:

Differences between observed incidence rates between CNR cohort 3 and the other cohorts can be used to assess whether a change in effectiveness due to a change in monitoring frequency can be considered. Unfortunately, enrollment in CNR cohort 3 is decreased during 1997-2001 period (3,480 in 2001 versus 12,632 in 1997). Also there was a higher loss to follow-up rate compare to than previous cohorts (50% versus 35%). These factors negatively impact for analysis of the cohort.

Ten patients in CNR cohort 3 developed agranulocytosis after 6 months of treatment. As shown in Table 2, the incidence rate of agranulocytosis during the first 6 months of treatment among patients who underwent weekly monitoring was 3.6 times the incidence measured between 6 and 12 months of treatment. These data support the premise that the risk is highest early in the course of therapy and declines thereafter. However, the limited enrollment / losses to follow-up prevent analysis of risk after 2 years of treatment. [Note, in CNR cohort 3 at treatment initiation exposure was 39,260 person-years diminishing to 22,204 person-years after 6 months of treatment and to 7,903 person-years after 2 years of treatment. This suggests a very high loss to follow-up rate. Therefore, after longer periods of treatment, the risk estimates are not only unstable but may be biased if loss to follow-up is associated with the risk of agranulocytosis.

Table 2. Life table for incidence of agranulocytosis in CNR cohort 3

Time interval (in years)	# of occurrences	# of patients left	Hazard rate (per 1,000 pt-weeks)	Lower 95% CI on hazard rate	Upper 95% CI on hazard rate
Agranulocytosis					
0-0.5	46	39260	0.0576	0.0409	0.0742
0.5-1	8	22209	0.0161	0.0050	0.0273
1-2	2	15936	0.0032	0.0000	0.0077
2-3	0	7903	0.0000	-	-
3-4	0	2638	0.0000	-	-
Severe leukopenia					
0-0.5	48	39260	0.0601	0.0431	0.0771
0.5-1	4	22204	0.0081	0.0002	0.0160
1-2	1	15934	0.0016	0.0000	0.0048
2-3	4	7903	0.0146	0.0003	0.0289
3-4	0	2638	0.0000	-	-

5. Projection estimates:

In the sponsor's report, an analysis of projected number of cases of agranulocytosis and severe leukopenia after reduction of WBC monitoring frequency from biweekly to monthly and to "no monitoring" was included (Table 3). These projected estimates were not based on data from cohort 3 alone, but incorporated data from CNR cohorts 1 and 2 as selected parameters from CNR cohort 3 were deemed unreliable due to small number of events. Based on the projected estimates, the "no monitoring" policy after 6 months of treatment led to higher incidence rates (5.81 /1,000 patient-years). In a separate submission in 1997, the sponsor projected an incidence rate for agranulocytosis of 0.93 per 1,000 patient-years associated with a change to biweekly monitoring after six months of treatment. However, the company has observed an incidence rate of 0.26 per 1,000 patient-years (or 0.37 per 1,000 patient-years based on a September 2002 submission). This discrepancy between expected and observed rates points to an important limitation of modeling and may be attributable to a number of other factors which affect the risk of agranulocytosis over the course of clozapine treatment.

Table 3. Projected incidence rates (per 1,000 patient-years) for agranulocytosis and severe leukopenia occur after 6 months of Clozaril therapy based on the timing of reduction in frequency of WBC monitoring in CNR cohort 3.

change in monitoring after	Biweekly (actual)	Monthly	No monitoring
agranulocytosis			
six months	0.26	1.68	5.81
one year	0.26	1.21	3.43
two years	0.26	0.6	1.52
severe neutropenia			
six months	0.33	3.68	8.51
one year	0.33	2.40	4.89
two years	0.33	0.90	1.52

6. Supplementary analysis:

The sponsor has provided a further analysis of the CNR database in an attempt to explain why the incidence of agranulocytosis has not increased in successive cohorts as expected. One possible explanation that has been offered is that CNR cohort 3 has an intrinsic lower risk for agranulocytosis than CNR cohorts 1 and 2. The sponsor compared age, sex, and ethnicity as well as the slope of WBC reduction during the prodrome (a period during which the WBC count declines before development of moderate leukopenia). The sponsor did not find any significant differences between cohorts with respect to the distribution of age, sex, or ethnicity. However, their analysis revealed that among patients who developed moderate leukopenia, patients in CNR cohort 3 had a slower rate of WBC reduction during the prodromal period compared to patients in CNR cohorts 1 and 2 (pooled analysis). This suggests that individuals in CNR cohort 3 may be less susceptible than patients in earlier cohorts.

The sponsor has also hypothesized that patients in latter cohorts may have stopped Clozaril treatment earlier, before development of moderate leukopenia, in comparison to earlier cohorts. The median WBC count at the time of discontinuation for patients in cohort 1 was 7,700 /mm^3, slightly higher than 7,400 /mm^3 as reported among patients in

cohort 2 and 3 (pooled analysis). One can argue that, the WBC count at the time cessation of treatment should be compared only for those patients whose reason of discontinuation was based on their health provider's advice. Unfortunately, reasons for discontinuation have not been collected in the CNR. It can be argued that a health provider may not rely on WBC counts alone in deciding whether to discontinue Clozaril treatment. [See Discussion]

Discussion:

A biweekly monitoring requirement was only implemented in cohort 3 for patients who were treated with Clozaril more than 6 months. Therefore, it may be useful to both analyze the data from cohort 3 to determine the impact of a change of monitoring frequency from a weekly to biweekly protocol on the incidence of agranulocytosis and to project the incidence rates of this adverse events if monitoring regimens that are less frequent than biweekly were to be implemented. However, in this cohort, there were only 10 cases of agranulocytosis among those treated with Clozaril for longer than 6 months. This small number of events does not permit a reliable projection of incidence rates for a model that is based on at least 4 parameters. Using data from other cohorts or sources raises an issue of comparability between cohorts (Cohort 3 may not be comparable with patients from earlier cohorts due to intrinsic differences in susceptibility; see below.)

For all patients treated with Cozaril, the weekly monitoring system within the first six months of therapy has not changed. Nevertheless, in successive cohorts, there has been a downward trend in the incidence of agranulocytosis, suggesting that other factors affect the risk of this adverse event. It is possible that these factors would also affect risk among patients who continue taking Clozaril longer than 6 months.

Two possible explanations for a reduction of the incidence rates of agranulocytosis in Clozaril-treated patients are increasing knowledge, experience and awareness of health providers about this drug; and the recent approval of other anti-psychotic drugs. In addition, patients with a relatively higher risk for agranulocytosis may be predisposed to receive generic form of clozapine (1997).

An increase in knowledge and experience of health providers related to risk factors for Clozaril-associated agranulocytosis or changes in response rate to clozapine are likely explanations for the observed reduction over time of risk for agranulocytosis. An increase in the number of publications that address factors associated with better responses to clozapine treatment and/or agranulocytosis may reflect increasing levels of knowledge among health providers. Recent onset of illness, [1-2] short total duration of hospitalization,[2] good functioning in the previous year,[3] and presence of EPS during typical neuroleptic treatment[4] have been reported to be associated with good responses to Clozaril treatment. In contrast, factors such as increasing age,[5] female sex,[5-6] coadministration of certain other drugs, and genetic susceptibility[7-8] (e.g. patients of Ashkentazi Jewish decent with the HLA-B38 phenotype) have been reported to be related to an increased risk of Clozaril-associated agranulocytosis. Health care providers may have increasingly monitored these and other factors in the treatment, and follow-up of patients treated with clozapine. Therefore, over time, a cohort of lower risk patients treated with clozapine may have emerged.

The approval of new antipsycotic drugs also may also explain such a reduction in the risk. Since 1990, several new antipsycotic drugs for which, agranulocytosis warnings in the labels do not appear, have been approved. Such alternate treatment, in combination with increased knowledge among health care providers about clozapine, might act synergistically to lower the rate of clozapine-associated agranulocytosis.

Finally, patients treated with the generic form of clozapine may be at higher risk for the development of agranulocytosis compare to those who are treated with the Clozaril-brand clozapine. The rationale for suggesting this possibility is that the socio-economically compromised patients receiving to treatment with generic brands may be more susceptible to agranulocytosis because of characteristics associated with lower income (e.g., age and duration of disease). Unfortunately, the CNR does not maintain the records of patients treated with generic form of clozapine. Therefore, a comparison of incidence rates between brand and generic forms of clozapine is not possible.

Limitations of comparability, representativeness, and stability of estimates would reduces the usefulness of data from CNR to project the risk of agranulocytosis associated with changing the monitoring frequency from a biweekly to a lower frequency. Estimates for a "worst case" and "best case scenarios" indicating likely boundaries of rates have been independently suggested by this reviewer.

In the worst-case scenario, patients would not be monitored after the first 6 months of treatment. Hence , after the initial treatment period, a patient's progression to agranulocytosis from moderate leukopenia would not be prevented by physician's intervention. In cohort 3, 230 cases of moderate leukopenia were identified (based on Table B, reported on February 12, 2003). The sponsor projected that an additional two cases of rapid onset of agranulocytosis would occur leading to a total of 232 cases; 232 in 27017 patient-years is equivalent to 8.6 per 1,000 patient-years. This estimate is somewhat higher than the worst case scenario calculated by the sponsor of 5.81 per 1000 patient-years (The sponsor has assumed that only 67% of moderate leukopenia cases would develop agranulocytosis).

In the best-case scenario based on data obtained from cohort 3 and a protocol of biweekly monitoring, the incidence rate for agranulocytosis after six months of treatment is 0.26 per 1,000 patients-years (260 / 1,000,000 patient-years). This rate is higher than the rate of background agranulocytosis that has been observed in the general population (1-15 /million persons/year).(1)

CONCLUSION

[1] A discussion of background rates for agranulocytosis in the general population and risk for drug-induced agranulocytosis for selected drug products is included in a memorandum dated July 7, 1997 by Dr. Judith Racoosin of HFD-120.

Projections of the incidence rates of agranulocytosis for patients undergoing either monthly monitoring or no monitoring after the first six months of treatment with clozapine which are based on data from the Clozaril National Registry (CNR) are subject to significant limitations in accuracy.

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